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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/070,295	09/09/2002	Menachem Rubinstein	RUBINSTEIN=7	2828

1444 7590 07/28/2008

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EXAMINER
CHANDRA, GYAN

ART UNIT	PAPER NUMBER
1646	

MAIL DATE	DELIVERY MODE
07/28/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/070,295	RUBINSTEIN ET AL.	
	Examiner	Art Unit	
	GYAN CHANDRA	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 May 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *5,9,11,12 and 15-18* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *5,9,11,12 and 15-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 5/1/2008 has been entered.

Status of Application, Amendments, And/Or Claims

The amendments of claim 9 have been made of record.

Claims 5, 9, 11-12 and 15-18 are pending.

Claims 5, 9, 11-12 and 15-18 are examined on the merit to the extent that they read on the elected invention of VEGF inhibitor – CSC.

Response to Arguments

Claim Rejections-maintained

Claim Rejections - 35 USC § 112-enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 5, 9, 11, 12 and 15-18 stand rejected under 35 U.S.C. 112, first paragraph-enablement for the reasons of record on pages 5-10 of the Office Action mailed on 2/13/2006 and on pages 3-5 of the Office Action mailed on 4/5/2007.

Claims 5, 9, 11, 12 and 15-18 are drawn to a method for inhibiting angiogenesis in mammals comprising administering to a subject a pharmaceutical composition comprising (i) leptin, (ii) a leptin fragment, (iii) a leptin homolog having 90% sequence identity with sequence of leptin, or (iv) a derivative of leptin or leptin homolog which has the activity of leptin, and optionally, an inhibitor of angiogenesis in a suitable dosage, (v) wherein angiogenesis inhibitor is a VEGF inhibitor, (vi) wherein the derivative said derivative has one or more chemical moieties attached to leptin, (vii) wherein said chemical moieties are water soluble polymers, and wherein said polymers are polyethylene glycol.

Applicants argue (page 2 of Response) that the animal model used in the instant invention (-ob/-ob mouse) is a customary way to establish a protein function. They reiterated their arguments that the addition of leptin to a leptin-deficient (ob/ob) mouse results in angiopoietin 2 and inhibition of angiogenesis in adipose tissue. Applicants argue that the reference Cao teaches leptin induces angiogenesis by measuring (i) capillary growth in the corneal model, and (ii) fenestration, and argue that the fenestration is different than capillary growth. Thus, appicants argue that Cao does not teach increase in capillary in adipose tissue. In support, Applicants provide Menachem's declaration and the reference Hanahan (Science, 277, 48-50, 1997).

Applicants arguments have been fully considered but they are not persuasive because the instant rejection is not based on the issue that the -ob/-ob KO mouse is not a proper model to study a gene function. The instant rejection is under 35 U.S.C. 112, first paragraph-enablement and as presented in the previous Office Action of 11/2/2007, the specification only teaches an -ob/-ob mouse where leptin inhibits angiogenesis. Further, the features upon which applicant relies (i.e., a method for inhibiting angiogenesis in -ob/-ob mouse) are not recited in the rejected claim(s). Cao et al teach that leptin induces angiogenesis (new blood vessels fenestration) in normal except in leptin deficient ob/ob mice (see abstract). Cao et al teach that wild type mouse have more capillaries that ob/ob mouse (Fig 3 and page 6392 right column). Further, the limitation "angiogenesis in adipose tissue" appears only in claim 18 and therefore, applicants arguments are not persuasive for claims 5, 9, 11,12 and 15-17. And, since the product of the prior art is identical to that required by the claims, the method will inherently lead to the same effect. See Ex parte Novitski 26 USPQ 1389 (BPAI 1993). It is well established in the art that leptin is an inducer of angiogenesis in normal mammal (IDS, Sierra-Honigmann et al, 1998; previously presented, Bouloumie et al., 1998 and previously presented, Cao et al. Proc. Natl. Acad. Sci. 98:6390-6395, 2001). Therefore, the effect of leptin on angiogenesis inhibition appears to be limited to ob/ob mice only. Applicants only argue the reference Cao but they do not argue the references Sierra-Hongamann and Boulooumie et al which support the state of art.The reference Hanahan teaches a pathway of cell proliferation and angiogenesis using VEGF and

other signaling molecules (e.g., ang1 or ang2). But the reference Hanahan does not establish that leptin does not promote angiogenesis in normal animal.

The declaration of Menachem states (i) that a knockout mouse is well accepted model to study a gene function and (ii) the reference Cao does not teach or suggest that leptin induces capillary growth in adipose tissue.

Menachem's declaration that a knockout mouse is well accepted model for studying a gene function is persuasive. However, the claims are not directed to leptin function in a –ob/-ob mouse. The instant claims are directed to "a method for inhibiting angiogenesis in mammals" and the art has established that leptin is an inducer of angiogenesis in normal mammal (IDS, Sierra-Honigmann et al, 1998; previously presented, Bouloumie et al., 1998 and previously presented, Cao et al. Proc. Natl. Acad. Sci. 98:6390-6395, 2001). Further, the reference Cao et al teaches that leptin (10ng/mL) clearly induces angiogenesis as evidenced by cornea model (Fig. 1). Regarding Menachem's declaration that Cao does not teach or suggest that leptin induces capillary growth in adipose tissue is not persuasive because Cao et al teach that the endothelial growth response to leptin is dose dependent (6391, Results, capillary endothelial cell growth and Fig. 1e). Cao et al teach that wild type mouse have more capillaries that ob/ob mouse (Fig 3 and page 6392 right column). And, since the product of the prior art is identical to that required by the claims, the method will inherently lead to the same effect. See Ex parte Novitski 26 USPQ 1389 (BPAI 1993). Thus, since the product of the prior art has the same chemical structure as that

described in the specification, it can be assumed that the product will inherently perform the claimed process. (See MPEP 2112.02). It is noted that Menachem is a co-inventor in this application. Further, it is noted that while the declaration Menachem discusses findings in terms of "-ob/-ob mouse", no data regarding inhibition of angiogenesis by administering leptin in a normal mouse is disclosed, making it difficult for the Examiner independently to draw conclusions. Also, no published work of other researchers showing leptin's inhibitory effect on angiogenesis in a normal mouse has been cited. Based on consideration of the totality of the evidence, it is proper to maintain the rejections.

Conclusion

No claim is allowed.

All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within

TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Gyan Chandra
Art Unit 1646
19 July 2008
Fax: 571-273-2922

/Robert Landsman/
Primary Examiner, Art Unit 1647